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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,006	SAMBROOK ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-57 and 59-74* is/are pending in the application.

4a) Of the above claim(s) *46-48,50,66-71 and 74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *38-45,49,51-57,59-65,72 and 73* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/362,314.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 5/29/2007, in reply to the Office Action mailed 12/27/2006, is acknowledged and has been entered. Claims 38 – 57 and 59 – 74 are pending, of which claims 46 – 48, 50, 66 – 71 and 74 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 38, 45, 55 and 61 have been amended. Claim 58 has been cancelled. Claims 38 – 45, 49, 51 – 57, 59 – 65, 72 and 73 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

All rejections not reiterated herein have been withdrawn as having been overcome by amendment.

Applicant's arguments filed 5/29/2007 have been fully considered but they are not persuasive for reasons set forth hereinbelow.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Itokazu *et al.* (*J. Biomed. Mater. Res.*, 1998, 39, p. 536 – 538) for reasons set forth in the Office Action mailed 12/27/2006.

Applicant argues on page 15 of the Response that Itokazu teaches the loading of a chemotherapeutic agent, MTX, into the pores of a porous apatite ceramic, and only experiments with two types of porous apatite ceramic are discussed: hydroxyapatite block having a porosity of 35 – 48% and a pore size range of 500 – 300 μm and β-tricalcium phosphate block having a porosity of 75 – 80% and a pore size of 100 – 400 μm. Applicant contends that claim 38 has been amended to require a ceramic carrier comprising hydroxyapatite block having a density of less than 30% theoretical, i.e. a porosity of more than 70%. However, independent claims 64 and 65 do not recite the identity of the ceramic carrier (i.e. does not distinguish between hydroxyapatite and β-tricalcium phosphate or any other ceramic), thus the claims stand rejected.

Claims 38 – 44, 51, 52, 61 – 63, 72 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Imura *et al.* (US 6,340,648) for reasons set forth in the Office Action mailed 12/27/2006.

Applicant argues on page 16 of the Response that while Imura discloses calcium phosphate porous sintered bodies with a porosity of 55 – 90% (i.e. a theoretical density of 10 – 45%), as regards hydroxyapatite bodies it discloses only articles having porosities of 65% (Example 3), 68% (Example 4) and 70% (Examples 1 and 2).

Applicant contends this is outside the range required by amended claim 38, i.e. less than 30% theoretical density.

This is non-persuasive because a reference is not limited to what is taught by the examples, patents are relevant as prior art for all that they contain (see MPEP 2123). The Imura reference clearly teaches that a calcium phosphate porous sintered body, including hydroxyapatite, having pores of a size within the claimed range and a porosity of 55% or more and 90% or less (i.e. a theoretical density of 10 – 45%), which is anticipatory to applicant's ranges of less than about 30%, as in instant claim 38, or from about 10 to about 30%, as in instant claim 44. See Imura claims 1 – 3. Furthermore, regarding Examples 1 and 2, Imura discloses a hydroxyapatite sintered body having a porosity of 70% (i.e. a theoretical density of 30%). Applicant's instant claim 38 is drawn to a "carrier comprising block hydroxyapatite and having a density of less than *about* 30% theoretical...". The recitation of "*about* 30%" is interpreted given its broadest reasonable interpretation to include slightly more and slightly less than 30%. Thus "less than *about* 30%" reads on 30%, because less than *about* (i.e. slightly more than) 30% would include 30%. This interpretation is also applicable to dependent claim 44, which teaches a range of from *about* 10% to *about* 30% theoretical density.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 61 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is unclear because claim 38 defines the carrier as hydroxyapatite, however claim 61, which is dependent upon claim 38 broadens the carrier to include any metal or metal oxide. Accordingly, the dependent claim fails to further limit the scope of the independent claim.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 38 – 45, 59, 61 – 63, 72 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith *et al.* (WO 98/15505).

Smith discloses porous ceramic articles. The ceramic is composed of struts, etc. (page 7). The articles are preferably prepared from hydroxyapatite (page 8, line 17). Pore sizes may range from 50 – 150 microns or greater than 150 microns (page 8, lines 6 – 7 and claim 14). The pore sizes in the formed article can be controlled to yield a material with a pre-determined pore size and level of interconnectivity. The porosity may be from 20% to 90% (page 9, line 16). Such an article having a highly microporous structure is produced if sintering is controlled, and has advantages such as it may be filled with drugs such as antibiotics or growth factors, to act as a slow release agent at the site of an implant. The formed article may be in a variety of shapes (granules, bars, cylinders, etc.) (pages 10, line 18 – page 11, line 5 and claim 15).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 38 – 45, 49, 51, 52, 61 – 65, 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Imura *et al.* (US 6,340,648) or Smith *et al.* (WO 98/15505), in view of Itokazu *et al.* (*J. Biomed. Mater. Res.*, 1998, 39, p. 536 – 538).

Imura teaches a calcium phosphate porous sintered body which comprises spherical pores communicating with one another substantially throughout the body, and with a porosity between 55 – 90% (i.e. a theoretical density of 10 – 45%) (abstract). The pore diameter is preferably 200 – 5000 μm (column 4, line 5). The device may be a carrier for drug delivery and gradual release (column 1, lines 5 – 10 and column 6, lines 63 – 67). The surface of the material is etched with acid by dipping the porous sintered body into acid and passing the acid into the pores, which results in remarkable etching of the surface of the body and uniform etching of the inner part of the calcium phosphate porous sintered body (column 6, lines 4 – 15). The ceramic material is calcium phosphate, and may be calcium phosphate hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$ (column 4, lines 46 – 50 and claim 3).

Smith discloses porous ceramic articles composed of struts, etc. (page 7). The articles are preferably prepared from hydroxyapatite (page 8, line 17). Pore sizes may range from 50 – 150 microns or greater than 150 microns (page 8, lines 6 – 7 and claim 14). The pore sizes in the formed article can be controlled to yield a material with a pre-determined pore size and level of interconnectivity. The porosity may be from 20% to

90% (page 9, line 16). Such an article having a highly microporous structure is produced if sintering is controlled, and has advantages such as it may be filled with drugs such as antibiotics or growth factors, to act as a slow release agent at the site of an implant.

Imura or Smith do not specifically teach the identity of the drug which is delivered via the carrier.

Itokazu teaches porous apatite ceramics (PAC), including β-tricalcium phosphate (TCP) and hydroxyapatite for the sustained release of a chemotherapeutic, methotrexate (MTX) (abstract). The MTX was loaded into the pores of the ceramic carrier via centrifugation (page 536).

Itokazu does not teach hydroxyapatite having a density less than about 30% theoretical as the porous apatite ceramic for local delivery of MTX.

It would have been obvious to one of ordinary skill in the art to utilize MTX as the drug which is deposited within the hydroxyapatite carriers of Imura or Smith. One would have been motivated to do so because Itokazu teaches similar chemotherapeutic agent-loaded porous apatite ceramics to be useful to fill grafts after curettage of bone tumor (Itokazu, page 536). One would have been motivated to utilize hydroxyapatite having a porosity within the claimed range, as taught by Imura or Smith in order to achieve a carrier with an optimal balance of a desirable MTX release profile and adequate mechanical strength because Imura and Itokazu both teach the importance of pore size and porosity in drug release and strength of the carrier (Imura column 3, line 37 – column 4, line 5; Itokazu, page 538, left column).

Claims 38 – 45, 51 – 54, 56 – 57, 59, 61 – 63, 72, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Genin *et al.* (US 6,767,550), in view of Imura *et al.* (US 6,340,648) or Smith *et al.* (WO 98/15505).

Genin teaches a hydroxyapatite based drug delivery implant for cancer treatment. Sustained release of the anti-cancer agents may be achieved after implantation at targeted sites (abstract). The ceramic component of the implant may be tricalcium phosphate, hydroxyapatite, etc. (column 2, lines 51 – 57). The implant has two layers, a first layer consisting of pure hydroxyapatite and the second layer contains hydroxyapatite, a bioresorbable material (i.e. collagen or polymer), and doxorubicin (an anti-cancer agent) (claim 1). The first layer may further comprise polymer or collagen (claim 4). The implant may be porous (claim 6). When the implant is porous, the pore size is between 1 μm – 3 mm, depending on the desired drug release profile (column 6, lines 35 – 40). Thus, Genin teaches a carrier which has an alternating agent-free layer and an agent-containing layer (i.e. the layers are different from the neighboring layer).

Genin fails to identify the specific density of the ceramic used in his porous ceramic implant. Thus, he does not teach that his anti-cancer drug delivery device has a density which is specifically less than 30% theoretical.

Imura discloses calcium phosphate porous sintered body which comprises spherical pores communicating with one another substantially throughout the body, and with a porosity between 55 – 90% (i.e. a theoretical density of 10 – 45%) (abstract), as set forth above. Such articles are used as carriers for drug delivery and gradual release systems (column 1, line 9).

Smith discloses porous ceramic articles which are preferably prepared from hydroxyapatite (page 8, line 17). Pore sizes may range from 50 – 150 microns or greater than 150 microns (page 8, lines 6 – 7 and claim 14). The pore sizes in the formed article can be controlled to yield a material with a pre-determined pore size and level of interconnectivity. The porosity may be from 20% to 90% (page 9, line 16). Such an article having a highly microporous structure is produced if sintering is controlled, and has advantages such as it may be filled with drugs such as antibiotics or growth factors, to act as a slow release agent at the site of an implant, as set forth above.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize a ceramic with a density within the claimed range in the drug delivery implant of Genin consisting of drug-containing and drug-free layers because Imura or Smith teach porous calcium phosphate bodies, such as hydroxyapatite, to be useful for such purposes. One would have been motivated to do so in preparing a ceramic with a desired release profile, because Genin specifically teaches that modification of the microstructure, morphology, and composition of the bioresorbable material (i.e. ceramic or polymer) allows for control of the drug release profile (abstract). Genin also teaches that his implants may be dense or porous and refers to tailoring the pore size in the porous implants depending on the desired drug release profile (column 6, lines 35 – 40). Because Genin is silent regarding the specific pore size and porosity of his carrier, therefore one would have been motivated to select and utilize the carriers of Imura or Smith, because Imura specifically teaches the importance of porosity / pore

size such as those which are instantly claimed in the determining the release properties of such materials (column 2, lines 40 – 49 and column 3, line 37 – column 4, line 5).

Claims 38 – 45, 51 – 57, 59, 61 – 63, 72, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Genin *et al.* (US 6,767,550), in view of Imura *et al.* (US 6,340,648) or Smith *et al.* (WO 98/15505), in further view of Brem *et al.* (US RE37,410).

Genin teaches a hydroxyapatite based drug delivery implant for cancer treatment. Sustained release of the anti-cancer agents may be achieved after implantation at targeted sites (abstract). The ceramic component of the implant may be tricalcium phosphate, hydroxyapatite, etc. (column 2, lines 51 – 57). The implant has two layers, a first layer consisting of pure hydroxyapatite and the second layer contains hydroxyapatite, a bioresorbable material (i.e. collagen or polymer), and doxorubicin (an anti-cancer agent) (claim 1). The first layer may further comprise polymer or collagen (claim 4). The implant may be porous (claim 6). When the implant is porous, the pore size is between 1 μm – 3 mm, depending on the desired drug release profile (column 6, lines 35 – 40). Thus, Genin teaches a carrier which has an alternating agent-free layer and an agent-containing layer (i.e. the layers are different from the neighboring layer).

Genin fails to identify the specific density of the ceramic used in his porous ceramic implant. Thus, he does not teach that his anti-cancer drug delivery device has a density which is specifically less than 30% theoretical.

Imura discloses calcium phosphate porous sintered body which comprises spherical pores communicating with one another substantially throughout the body, and with a porosity between 55 – 90% (i.e. a theoretical density of 10 – 45%) (abstract), as set forth above. Such articles are used as carriers for drug delivery and gradual release systems (column 1, line 9).

Smith discloses porous ceramic articles which are preferably prepared from hydroxyapatite (page 8, line 17). Pore sizes may range from 50 – 150 microns or greater than 150 microns (page 8, lines 6 – 7 and claim 14). The pore sizes in the formed article can be controlled to yield a material with a pre-determined pore size and level of interconnectivity. The porosity may be from 20% to 90% (page 9, line 16). Such an article having a highly microporous structure is produced if sintering is controlled, and has advantages such as it may be filled with drugs such as antibiotics or growth factors, to act as a slow release agent at the site of an implant, as set forth above.

Genin, Imura or Smith do not teach CPP.SA as a biodegradable support polymer which is contained within the pores of the carrier.

Brem teaches biodegradable polymer matrices for the controlled local delivery of chemotherapeutic agents (abstract). Examples of such biodegradable polymers include natural polymers such as collagen, gelatin, etc. or synthetic polymers, preferably CPP-SA (column 5, lines 24+).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize a ceramic with a density within the claimed range in the drug

delivery implant of Genin consisting of drug-containing and drug-free layers because Imura or Smith teach porous calcium phosphate bodies, such as hydroxyapatite, to be useful for such purposes. One would have been motivated to do so in preparing a ceramic with a desired release profile, because Genin specifically teaches that modification of the microstructure, morphology, and composition of the bioresorbable material (i.e. ceramic or polymer) allows for control of the drug release profile (abstract). Genin also teaches that his implants may be dense or porous and refers to tailoring the pore size in the porous implants depending on the desired drug release profile (column 6, lines 35 – 40). Because Genin is silent regarding the specific pore size and porosity of his carrier, therefore one would have been motivated to select and utilize the carriers of Imura or Smith, because Imura specifically teaches the importance of porosity / pore size such as those which are instantly claimed in the determining the release properties of such materials (column 2, lines 40 – 49 and column 3, line 37 – column 4, line 5). It would have been further obvious to substitute CPP.SA for collagen as the bioresorbable material in the carrier of Genin (claim 1 or column 7, lines 17 – 21) because Genin teaches collagen or bioresorbable polymers to be useful, and because Brem teaches that CPP-SA is a biodegradable polymer which may be used as a functional equivalent to collagen or other polymers for the release of a drug by diffusion, degradation of polymer, or combinations thereof (column 5, lines 24+).

Claims 38 – 44, 51, 52, 59 – 63, 72 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Imura (US 6,340, 648) in view of Hakamatsuka (US 5,318,779).

Imura teaches a calcium phosphate porous sintered body which comprises spherical pores communicating with one another substantially throughout the body, and with a porosity between 55 – 90% (i.e. a theoretical density of 10 – 45%) (abstract). The pore diameter is preferably 200 – 5000 μm (column 4, line 5). The device may be a carrier for drug delivery and gradual release (column 1, lines 5 – 10 and column 6, lines 63 – 67). The surface of the material is etched with acid by dipping the porous sintered body into acid and passing the acid into the pores, which results in remarkable etching of the surface of the body and uniform etching of the inner part of the calcium phosphate porous sintered body (column 6, lines 4 – 15). The ceramic material is calcium phosphate, and may be calcium phosphate hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$ (column 4, lines 46 – 50 and claim 3).

Imura does not teach coating the surface of the porous body with a polymer to further control release of the drug contained therein.

Hakamatsuka teaches a drug-impregnated ceramic to be embedded in a living body. The porous ceramic has pores with a size of 10 – 300 μm, a drug impregnating the ceramic pores, and a surface layer for controlling the release of the drug (abstract).

Hakamatsuka does not specifically teach that the ceramic is hydroxyapatite having a density of less than 30% theoretical.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to include a collagen polymer on the porous calcium phosphate, including hydroxyapatite (see Ex. 1) bodies of Imura having a porosity which is preferably in the range of 60 – 85% and pore size which is preferably from 100 – 4000 μm (column 2, lines 40 – 48) because such materials are useful as carriers for drug delivery and gradual release systems (column 1, line 9). One would have been motivated to do so because Hakamatsuka specifically teaches that such an exterior coating layer can be used for further controlling release of a drug from a similar porous ceramic material (column 2, line 16).

Conclusion

No claims are allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER